REMARKS/ARGUMENTS

Claim 28 is pending in this application. No new matter is added.

In support of the remarks and arguments stated *infra*, Applicants reference the Declaration of Dror Harats under 37 C.F.R. §1.132 first filed with Applicants December 7, 2005 Amendment and Response and re-filed with Applicants September 25, 2008 Response, which was entered into the record in the instant Final Office Action. Applicants also reference the Declaration of Dror Harats under 37 C.F.R. §1.132 filed with Applicants August 31, 2006 Amendment and Response, which was entered into the record and considered by the Examiner in the Final Office Action mailed on November 29, 2006.

Supplemental Information Disclosure Statement

The Examiner stated that the references C47, C52 and C61 submitted in Applicants September 25, 2008 Supplemental Information Disclosure Statement were not considered. Specifically, the Examiner stated that these non considered references were incomplete (missing figures) or contained illegible figures.

Applicants have resubmitted complete copies of these references, noted as C91-C93, in the Supplemental Information Disclosure Statement accompanying this Response and respectfully request full consideration of these references by the Examiner.

Rejections under 35 U.S.C. §112, first paragraph

Enablement

Claim 28 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

The Examiner states that the specification does not disclose how to use the claimed method to treat or prevent atherosclerosis in humans *in vivo* using an oral tolerance inducing amount of oxidized LDL. The Examiner further states that it is unpredictable whether human disease can be treated via inducing oral tolerance to a disease antigen. *See*, Final Office Action at pages 2-6. In support of the rejection, the Examiner recites *In re Wands*, 858 F.2d 731, 737

(Fed. Cir. 1988) factors (5), (7), (3) and (2) against claim 28 at pages 3-4 of the Final Office Action. Applicants traverse.

State of the Prior Art (Wands Factor 5) and Predictability or Unpredictability of the Art (*Wands* Factor 7)

The Examiner states that regarding *Wands* factors (5) and (7), there is a high unpredictability in the art. Specifically, the Examiner cites Spack et al. *Expert Opin. On Invest. Drugs*, 6:1715-1727, 1997 ("Spack") and McKown et al., *Arthritis and Rheum.* 42:1204-1208, 1999 ("McKown") to show that it is unpredictable whether human disease can be treated via the induction of oral tolerance to a disease antigen. *See*, Final Office Action at pages 4-5.

Applicants submit that pending claim 28 does not recite or require the induction of oral tolerance as stated by the Examiner. In fact, claim 28 is not directed to the induction of oral tolerance at all; rather, claim 28 is directed to a method of treating atherosclerosis by administering a therapeutically effective amount of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier for oral administration. As such, the Examiner's arguments regarding the unpredictability of disease treatment via inducing oral tolerance to a disease antigen, including the discussion of McKown and Spack is misplaced and improper.

Applicants have previously argued in the December 7, 2005 Amendment and Response, August 31, 2006 Amendment and Response and the In-Person-Interview conducted on November 15, 2005 that the claims are directed to treating atherosclerosis and do not recite or require the induction of oral tolerance. However, the Examiner has stated that although the claims are not directed to a specific mechanism of action, the disclosure indicates that the claimed method works via oral tolerance and that the disclosure is sufficient to maintain the enablement rejection under 35 U.S.C. §112, first paragraph. *See*, Final Office Action at page 5 and the Office Action mailed March 3, 2006 at page 7.

The Examiner's assertion is incorrect. It is well recognized under U.S. law, that it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works. *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989). It is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of

his invention rests, nor is the inventor's theory or belief as to how the invention works a necessary element in the specification to satisfy the enablement requirement. *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983). A patent applicant need only teach how to achieve the claimed result, even if the theory of operation is not correctly explained or even understood. *In re Isaacs,* 347 F.2d 887, 892, 146 USPQ 193, 197 (C.C.P.A. 1965). Applicants submit that the instant application discloses a method of treating atherosclerosis by administering a therapeutically effective amount of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier for oral administration and thus satisfies the how-to-use requirement of 35 U.S.C. §112, first paragraph, irrespective of whether the claimed method works via oral tolerance or another unidentified mechanism.

The Presence or Absence of Working Examples (*Wands* Factor 3)

The Examiner states that regarding *Wands* factor (3), while the specification provides an example in a mouse model, there were copious amounts of mouse research that suggested that while oral tolerance could be used to treat multiple sclerosis and rheumatoid arthritis in such models, said diseases were not successfully treated in humans using oral tolerance. The Examiner again cites McKown and Spack to support this assertion. *See*, Final Office Action at pages 4-5.

As described *supra*, claim 28 is not directed to the induction of oral tolerance and is not directed to the treatment of multiple sclerosis or rheumatoid arthritis and the citation of Spack and McKown is not relevant to the currently recited invention. The instant invention and the additional data generated using the teachings of the specification and reported in the December 7, 2005 Harats § 1.132 Declaration, attached hereto, readily demonstrate to one of ordinary skill in the art how to make and use the present invention to treat atherosclerosis by oral administration of isolated human oxidized LDL.

Specifically, the instant specification and the additional data supplied in the December 7, 2005 Harats § 1.132 Declaration provides a working example that demonstrates the successful treatment of atherosclerosis in an LDL-receptor deficient mouse by oral administration of isolated human oxidized LDL. *See*, Specification at, *e.g.*, page 15, lines 20-29; and page 18, line 18 to page 19, line 31. It is well recognized in the art that the LDL-receptor deficient mouse is

the preferred animal model to evaluate the effects of pharmacologic agents on atherosclerosis. LDL-receptor deficient mice, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis. *See*, August 31, 2006 Harats § 1.132 Declaration at ¶ 5-6 attached hereto.

Specifically, the use of animal models (*i.e.* murine models) to evaluate the effects of pharmacologic agents on atherosclerosis was well recognized in the art when the instant application was filed (*See, e.g.*, Bocan, *Curr. Pharm. Des.* 4(1):37-52, 1998); and, the LDL-receptor deficient mouse was recognized in the art as a preferred model of atherosclerosis at the time of the instant application. (*See, e.g.*, Ishibashi et al., *J Clin Invest.* 92:883–893, 1993; Lichtman *et al.*, *Arterioscler. Thromb. Vasc. Biol.* 19(8):1938-44, 1999; Maron, R. *et al.*, *FASEB J.* 14:A1199-(Abstr.), 2000). Moreover, mice having targeted inactivation of the apolipoprotein E (ApoE) gene and of the LDL-receptor gene, under appropriate conditions, develop complex atherosclerotic lesions and provide practical atherosclerotic mouse models and are the most utilized model to study lipids and atherosclerosis. *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 6.

To further support the rejection, the Examiner cites Wouters et al. *Clin. Chem. Lab. Med.* 43(5): 470-479, 2005 ("Wouters") and states that Wouters, discloses that the LDL-receptor mouse displays cholesterol metabolic pathways not found in humans and as a consequence "this route can serve as a backup mechanism for lipoprotein clearance in LDL-receptor mice, yielding unforeseen side effects." *See*, Final Office Action at page 6. Although the LDL-receptor deficient mouse is not the optimal model for genetic human familial hypercholesterolemia, it is one of the most predictable models for human atherosclerosis and the likelihood of new molecules to work as anti-atherosclerosis drugs in humans is high (*See, e.g.*, Babaei *et al.*, *Cardiovasc Res.* 48(1):158-67, 2000; Burleigh *et al.*, *Biochem Pharmacol.* 70(3):334-42, 2005; Chen *et al.*, *Circulation.* 106(1):20-3, 2002; Collins *et al.*, *Arterioscler Thromb Vasc Biol.* 21(3):365-71, 2001; Cyrus *et al.*, *Circulation.* 107(4):521-3, 2003; Elhage *et al.*, *Am J Pathol.* 167(1):267-74, 2005; Li *et al.*, *J Clin Invest.* 106(4):523-31, 2000; Napoli *et al.*, *Proc Natl Acad Sci U S A.* 99(19):12467-70, 2002). Human atherosclerotic plaques are infiltrated with lymphocytes and display an inflammatory phenotype that includes expression of pro-

inflammatory cytokines. In this sense the LDL-receptor deficient mice have plaques similar to those of humans containing a significant number of lymphocytes (*See, e.g.*, Roselaar *et al.*, *Arterioscler Thromb Vasc Biol.* 16(8):1013-8, 1996). Moreover, therapeutic strategies that apply for atheroprotection in humans are similarly successful in LDL receptor deficient mice and may not be so in ApoE knockout mice (*See, e.g.*, Wang *et al.*, *Atherosclerosis.* 162(1): 23-31, 2002). These findings indicate that plaques developing in LDL receptor deficient mice may be more relevant to human atherosclerosis than other non-human models and thus, it is one of the most widely employed models for drug development in the field of atherosclerosis. *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 6.

The Amount of Direction or Guidance Presented (*Wands* Factor 2)

The Examiner states that regarding *Wands* factor (2), there is no disclosure in the specification as to what doses would be used to induce the functional parameters recited in the claim which are related to properties of the oral tolerance induction mechanism. *See*, Final Office Action at pages 4-6.

Once again, as described in detail *supra*, claim 28 is not directed to the induction of oral tolerance but rather are directed to a method of treating atherosclerosis by oral administration of an enteric coated tablet or granule composition comprising isolated human oxidized LDL and a pharmaceutically acceptable carrier

Applicants have provided working examples that demonstrate the successful treatment of atherosclerosis by oral administration isolated human oxidized LDL in an LDL-receptor deficient mouse and the LDL-receptor deficient mouse is the most art-recognized model of the biochemical and morphological effects of atherosclerosis. Further, the working examples provide a range of concentrations of the composition to treat atherosclerosis (*See, e.g.*, page 18, lines 27-29; page 19, lines 18-19). Applicants assert that one of ordinary skill in the art, using the teachings of the instant invention, would be able to determine the corresponding doses useful in other species, including humans, without undue experimentation. The specification need not disclose what is well known in the art. *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385,

231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). *See*, December 7, 2005 Harats § 1.132 Declaration at ¶ 7-8.

As described *supra*, Applicants have provided several working examples, both in the specification and additional data confirming the results described in the specification, and demonstrated successful treatment of atherosclerosis by oral administration of isolated human oxidized LDL. Therefore, Applicants assert that one of ordinary skill in the art, using the teachings of the instant invention would be able to readily determine how to make and use the present invention and respectfully request withdrawal of the instant rejection of claim 28 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

On the basis of the foregoing amendment and remark, Applicants respectfully submit that the pending claims are in condition for allowance. Should any questions or issues arise concerning this application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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